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The GUCY2C Tumor Suppressor is the Nexus of a Paracrine Hormone Axis Preventing Radiotherapy-Induced Gastrointestinal (GI) Toxicity

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The GUCY2C Tumor Suppressor is the Nexus of a Paracrine Hormone Axis Preventing Radiotherapy-Induced Gastrointestinal (GI) Toxicity

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Purpose/Objective

Radiation-induced GI toxicity is the primary dose limitation compromising therapy in cancer patients treated with radiation therapy. GUCY2C is the intestinal receptor for diarrheagenic bacterial enterotoxins and the endogenous paracrine hormones guanylin and uroguanylin. Following genomic insult, cyclic (c)GMP produced by ligand activation of GUCY2C enhances DNA damage sensing and repair in intestinal cells. Here, we show that the GUCY2C-cGMP axis mediates p53-dependent radioprotection of intestinal epithelial cells.

Materials/Methods

Following total body irradiation (TBI) of *Gucy2C*$^{+/+}$ (wild type; n=3) and *Gucy2C*$^{-/-}$ (knockout; n=3) mice with 0, 5 and 10 Gy, intestines were formalin-fixed. Cell proliferation, apoptosis and DNA double strand breaks were quantified by immunohistochemistry using antibodies to Ki-67, cleaved caspase 3 and γ-H2AX, respectively. *Gucy2C*$^{+/+}$ (n=29) and *Gucy2C*$^{-/-}$ (n=38) mice were exposed to 13-18Gy TBI inducing lethal GI toxicity and survival followed up to 10d. In vitro, HCT116 (p53 wild type) and HCT116p53$^{-/-}$ (p53 null) human colon cells were treated with cGMP for 3 d, followed by 10, 30 and 50 Gy of ionizing radiation (IR).

Results

Gucy2C$^{-/-}$ mice exhibited accelerated death reflecting TBI-induced GI toxicity compared to *Gucy2C*$^{+/+}$ mice (median survival: 7 d, *Gucy2C*$^{+/+}$ mice; 5 d, *Gucy2C*$^{-/-}$ mice). The hazard ratio for death in *Gucy2C*$^{-/-}$ mice was 2.17 (95% confidence interval: 1.17 - 4.01, $p = 0.0133$ by the log-rank test). Reduced survival in *Gucy2C*$^{-/-}$ mice was associated with a 28% increase in crypt cell apoptosis ($p = 0.09$). Conversely, HCT116 cells preconditioned with cGMP resisted IR-induced cell death (12% cell death in cGMP-treated cells vs. 6% in control cells at 20 Gy; 17% vs. 10% at 40 Gy; 47.5% vs. 8% at 80 Gy). Protection by cGMP preconditioning was p53 dependent, and cGMP did not reduce IR-induced cell death in HCT116p53$^{-/-}$ cells (21.5% cell death in cGMP-treated cells vs. 25% in control cells at 20 Gy; 26% vs.19% at 40 Gy).

Conclusion

Eliminating the GUCY2C-cGMP axis increased radiation-induced intestinal DNA damage, crypt cell apoptosis, and lethal GI toxicity in *Gucy2C*$^{-/-}$, compared to *Gucy2*$^{+/+}$, mice. Conversely, GUCY2C downstream signaling in human colon cells *in vitro* attenuated radiation-induced cell death in a p53-dependent fashion. These observations suggest that the GUCY2C-cGMP axis maintains genomic integrity by amplifying DNA damage sensing and repair in the intestine following exposure to IR, protecting against lethal radiation-induced GI toxicity. They underscore the potential of oral administration of GUCY2C ligands for targeted radioprotection of intestinal epithelia to prevent IR-induced GI toxicity to improve the management of cancer therapy.